Heart failure in 10 years time: focus on pharmacological treatment

J J V McMurray

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Though the last decade has seen three major breakthroughs in chronic heart failure (CHF) treatment (with angiotensin converting enzyme (ACE) inhibitors,[1 2] β blockers,[3–5] and spironolactone[6]), the outlook of patients with this condition remains very poor. Even the relatively young, highly selected, patients taking part in clinical trials have a bad prognosis despite the best currently available treatment. For example, 7.2% of the metoprolol group in the MERIT-HF study (that is, patients receiving β blocker, ACE inhibitor, diuretic, and often digoxin treatment) died within one year of follow up and 32% died or were hospitalised at least once.[3 7] In the broader population the outlook of patients with CHF is much worse.[8] In one part of the UK, 45% of patients died within one year of discharge from their first ever hospital admission with heart failure.[8] The case fatality rate reached 77% within five years and the medial survival of a man discharged after his first heart failure hospitalisation was only 1.47 years. Not only are mortality and morbidity discouragingly and persistently high, but quality of life remains very impaired and the symptom burden of CHF is great. Clearly, more and/or better treatments are needed.

This is all the more so because the burden of CHF is set to increase substantially in coming years. Because populations are aging and survival from the underlying causes of CHF (coronary heart disease and hypertension) is increasing, the incidence and prevalence of CHF will increase. Indeed, in the UK, the prevalence is expected to increase by about 40% in the next two decades.

FUTURE THERAPEUTIC STRATEGIES IN CHF: THE NEUROHUMORAL HYPOTHESIS AS THE BASIS OF TREATMENT

Where should we look for new treatments? To date, the best framework we have for understanding heart failure is what has become known as the "neurohumoral hypothesis", first developed in the early 1980s and much modified since (fig 1).[9] Essentially, this paradigm identifies a key contributing role for neurohumoral factors in the pathophysiological progression of heart failure. Until recently, the focus has been on the importance of detrimental mediators such as the renin-angiotensin-aldosterone and sympathetic nervous systems. According to the neurohumoral model of heart failure, inhibition of the actions of these detrimental mediators should break into the neurohumoral "vicious cycle" of heart failure, thereby slowing down the relentless clinical progression that characterises the syndrome. The impressive reductions in morbidity and mortality with ACE inhibitors, spironolactone, and β blockers have all but proved the neurohumoral hypothesis.[1–7] Consequently, the identification and antagonism of the effects of other potentially detrimental "humoral" factors is one timely avenue to future therapeutic success in heart failure. More recently, we have also come to recognise that there are neurohumoral factors with potentially beneficial effects in heart failure, and augmentation of the action of these might also represent a useful therapeutic strategy in CHF. The best recognised factors of this type are the natriuretic peptides, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which are secreted in increased quantities by the failing heart. Indeed, CHF can be thought of as a state of neurohumoral imbalance, with a relative excess of vasoconstrictor, sodium/water retaining and growth promoting factors (for example, angiotensin II) over other factors having the opposite effects (for example, ANP and BNP). The optimum pharmacological strategy might be to correct this imbalance. Dual ACE/neutral endopeptidase (NEP) inhibitors (see below) are the first example of new drugs with this sort of action.

NEW PHARMACOLOGICAL AGENTS IN PHASE III CLINICAL TRIALS
Dual NEP/ACE ("vasopeptidase") inhibitors
Neutral endopeptidase (NEP), or neprilysin, is an enzyme which is present in many tissues including the heart, blood vessels, and kidneys.[10] NEP is best known as the enzyme that degrades the natriuretic peptides (or at least ANP and BNP), though it probably metabolises many other factors including angiotensin II, endothelin-1, adrenomedullin, and bradykinin. The major effect of systemic NEP inhibition is elevation of circulating concentrations of ANP and BNP, hormones with vasodilator, natriuretic, diuretic, anti-mitogenic and renin-angiotensin-aldosterone suppressing actions.[11 12] These effects, not surprisingly, are of potential benefit in heart failure. Early studies with NEP inhibitors in heart failure were encouraging, demonstrating favourable haemodynamic and neurohumoral effects and improvements in exercise tolerance.[13–15] Puzzlingly, these agents appeared to be ineffective in hypertension, possibly because of their inhibitory effect on angiotensin II breakdown. In other words, the beneficial effect of inhibition of natriuretic peptide degradation was counteracted by concomitant increases in angiotensin II. This, plus the unexpected toxicity related to ecadotril,[16] were factors stopping further development of NEP inhibitors in heart failure. More recently, molecules that inhibit *both* ACE and NEP have started to undergo investigation in heart failure.[10] The lead compound in this class is omapatrilat which is also an effective antihypertensive. A number of studies with omapatrilat have shown favourable haemodynamic and neurohumoral effects in heart failure.[17 18]

More intriguingly still, omapatrilat has been compared to lisinopril in the prospective randomised, double blind, IMPRESS trial.[18] In this parallel group study, 573 patients with New York Heart Association (NYHA) functional class II–IV heart failure, already receiving an ACE inhibitor, were randomly assigned to 40 mg omapatrilat daily or 20 mg lisinopril daily for 24 weeks. The primary end point, improvement in treadmill exercise time, was not different between groups. Overall, however, there were fewer morbid or adverse events indicative of worsening heart failure in the omapatrilat group. Two fairly standard composite end points favoured

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omapatrilat, one significantly so.[18] Of interest, a greater frequency of significant increases in blood urea nitrogen and creatinine were observed in the lisinopril than in the omapatrilat group.

To date, the only concern about omapatrilat has been that its use might be associated with a higher incidence and greater severity of angioedema than observed with ACE inhibitors.[19] This is not surprising, given that omapatrilat inhibits enzymatic pathways degrading bradykinin.[20] Initiation of treatment at a low dose and slow dose up-titration may minimise the risk of angioedema.

A definitive trial with omapatrilat in heart failure was recently completed. OVERTURE was a prospective, randomised, double blind comparison of omapatrilat to enalapril, given in a dose of 10 mg twice daily, in over 5500 patients with chronic heart failure. The primary end point was death or hospitalisation for worsening heart failure, though this trial was also powered to detect a clinically relevant difference in all cause mortality between treatments. Omapatrilat was not significantly superior to enalapril with respect to the primary end point, though it was with respect to an important secondary one.

Novel sympathetic nervous system inhibitors

Though β blockers have proved to be a highly effective treatment for heart failure, other antisympathetic nervous system interventions have either had a neutral survival effect or actually increased mortality.[21–24]

Nevertheless, the success of β blockers has encouraged the continued development of alternative anti-adrenergic strategies.[3–5 7]

Nolomirole is a pro-drug, the active metabolite of which is a selective presynaptic agonist for DA_2 dopaminergic and $α_2$ adrenergic receptors, actions which should reduce noradrenaline (norepinephrine) release.[25] Nolomirole is being compared to placebo in a large morbidity–mortality trial known as the echo cardiography and heart outcome study (ECHOS).

Endothelin receptor antagonist and other anti-endothelin agents

The endothelins are a family of three 21 amino acid peptides of which endothelin-1 (ET-1) is most abundant in the human cardiovascular system.[26 27] Endothelin-1 (ET-1) has a range of biological actions not dissimilar to angiotensin II, though on a molar basis it is much more potent—for example, it is 10 times as powerful a vasoconstrictor as angiotensin II in small human resistance arteries.[26 27] These effects, which include vasoconstriction, antinatriuretic and antidiuretic activity, a mitogenic action, and positive inotropism are, like those of angiotensin II, potentially harmful in heart failure. As with the activation of the renin-angiotensin-aldosterone system, there is evidence of increased endothelin production in heart failure, at least in the myocardium. Plasma concentrations of ET-1 are also increased.[28 29] Higher concentrations are associated with a worse symptom status, more depressed left ventricular systolic function, greater derangement of systemic and pulmonary haemodynamics, and a worse clinical outcome.[26 27] Patients with higher plasma ET-1 concentrations are more likely to require heart transplantation and are more likely to die.[30 31] Indeed, some studies have shown that plasma ET-1 concentration is a stronger, independent, predictor of survival than any other factor.[30 31] While these associations support the view that ET-1 may contribute to the pathophysiology of heart failure, especially in the light of the neurohumoral hypothesis, proof of such a role can only come from demonstrating that anti-endothelin interventions improve clinical outcome.

The anti-endothelin agents most advanced in development are the endothelin receptor antagonists.[32 33] Two broad types of endothelin receptors are recognised, the ET_A and ET_B

receptor.[26 27] The ET_B receptor is present on both endothelial cells and vascular smooth muscle cells (as well as in other tissues).[26 27] Endothelial ET_B receptors mediate vasodilation (via nitric oxide and possibly prostaglandins) whereas vascular smooth muscle ET_B receptors cause vasoconstriction. ET_A receptors in vascular smooth muscle are also vasoconstrictors. Both ET_A selective and non-selective (or "dual") $ET_{A/B}$ receptor antagonists are in clinical development. Indeed, a large number of ET receptor antagonists have already been studied in patients with heart failure.[34–36] To date, it is mainly acute dosing studies with invasive haemodynamic measurements that have been performed. These show that ET receptor antagonists have favourable acute haemodynamic effects, much as one would expect.[37–41] Chronic dosing haemodynamic studies have also been carried out with bosentan and darusentan, showing maintenance or even enhancement of the acute effect.[42] At least two relatively small pilot efficacy–safety studies examining a "clinical status" end point have been carried out with bosentan (used in a high dose) and enrasentan (both dual $ET_{A/B}$ receptor antagonists). Significant adverse events were encountered in both studies and those led to the early termination of the bosentan trial. Two larger trials with lower dose bosentan (the same dose recently shown to be effective in pulmonary hypertension) have just completed follow up (ENABLE-1 and ENABLE-2). A prospective pooling of these trials had been planned to look at the effect of bosentan on the combined end point of death or heart failure hospitalisation. Bosentan was not significantly superior to placebo and was associated with an early increase in the risk of worsening heart failure.
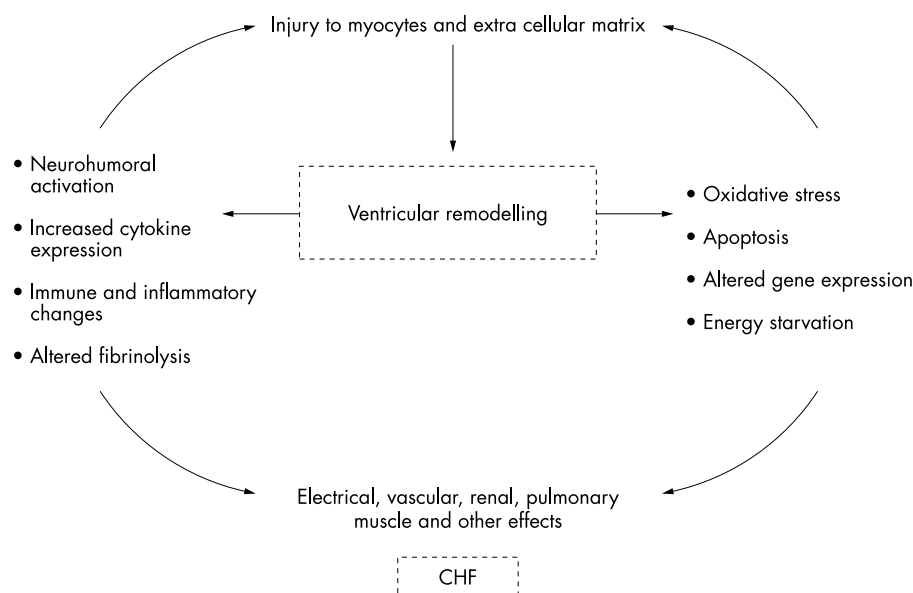
Cytokine antagonists

That increased plasma concentrations of proinflammatory cytokines are found in chronic heart failure has been recognised for over a decade.[43 44] Initially, it was thought that the best recognised of these mediators, tumour necrosis factor, might be important in the development of cardiac cachexia. Subsequently, it was suggested that cytokines may be more generally important in heart failure.[45–48] This view has been reinforced by the finding of a selective increase in production of tumour necrosis factor α in the failing human myocardium. The suggestion that cytokines might have multiple, potentially detrimental, actions in heart failure led to the development of the "cytokine hypothesis", which can be regarded as an extension of the earlier "neurohumoral hypothesis" of heart failure.[47] Indeed, heart failure seems to be a syndrome characterised by generalised, low level, inflammation with an increase in other inflammatory mediators as well as cytokines.[45–49]

As with hormonal and peptide factors, increased plasma concentrations of cytokines are associated with more advanced symptomatic and functional impairment, greater haemodynamic derangement, poorer left ventricular systolic function, and a worse prognosis.[45–48] That these relationships might be causal is supported not only by the known actions of cytokines but by animal experiments. Chronic tumour necrosis factor α infusion can cause left ventricular dilatation and systolic failure. Transgenic mice overexpressing the gene for tumour necrosis factor α develop a dilated cardiomyopathy and have a reduced life expectancy.[50]

Though much is still not known about cytokine activation in heart failure—for example, what initiates it—studies using anticytokine interventions have already been conducted.[45–48]

One of the first interventions was undertaken with pentoxifylline which appears to inhibit tumour necrosis factor α production.[51 52] Two studies, from the same centre, with this agent have reported improvements in left ventricular ejection fraction and functional status.

More recently, another non-specific anti-inflammatory intervention, intravenous immunoglobulin, has also been

Injury to myocytes and extra cellular matrix

- Neurohumoral activation
- Increased cytokine expression
- Immune and inflammatory changes
- Altered fibrinolysis

Ventricular remodelling

- Oxidative stress
- Apoptosis
- Altered gene expression
- Energy starvation

Electrical, vascular, renal, pulmonary muscle and other effects

CHF

Figure 1 The "neurohumoral" model of heart failure. Adapted from McMurry J, Pfeffer MH. *Circulation* 2002;**105**:2099–106.

reported to improve left ventricular function and, in support of this, reduce N terminal pro-ANP.[49] These changes were accompanied by striking anti-inflammatory effects on cytokines and their receptors

The most interesting development of all, however, in this field is the bioengineering of specific anticytokine interventions. The lead compound in this field is etanercept, or recombinant human soluble tumour necrosis factor receptor, which is a dimeric fusion protein consisting of the extracellular portion of the human p75 tumour necrosis factor receptor linked to the Fc portion of type 1 human immunoglobulin.[53] Etanercept binds and inactivates soluble and cell bound tumour necrosis factor α. Etanercept has a long half life (median approximately five days) and is administered by subcutaneous

injection. Etanercept is already approved world wide for the treatment of rheumatoid arthritis.

Two parallel trials with etanercept have been undertaken in North America (RENAISSANCE) and Europe and Australasia (RECOVER). Each was to examine the effect of etanercept on clinical status, and a prespecified pooling of both studies (RENEWAL) would have had sufficient statistical power to determine whether or not etanercept had a clinically important effect on the composite end point of death or hospitalisation with worsening heart failure. These studies were recently stopped prematurely, because of "futility". Full data are not available at the time of writing. We do not yet know if the hypotheses were wrong, the drug was ineffective or the trial design flawed. However, another placebo controlled study,

Table 1 Ongoing and planned trials of pharmacological agents in chronic heart failure

Trial acronym/name*	Treatment comparisons†
Low LVEF chronic heart failure	
Neurohumoral antagonists	
CHARM Alternative	Placebo *v* candesartan (ACE inhibitor intolerant patients)
CHARM Added	Placebo *v* candesartan (ACE inhibitor treated patients)
COMET	Carvedilol *v* metoprolol
ENABLE	Placebo *v* bosentan
ECHOS	Placebo *v* nolomirole
OVERTURE	Enalapril *v* omapatrilat
SENIORS	Placebo *v* nebivolol (patients >70 years)
Cytokine antagonists	
RENEWAL (RECOVER‡ and RENAISSANCE)	Placebo *v* etanercept
Antithrombotic agents	
WATCH	Warfarin *v* aspirin *v* clopidogrel
Inotropic agents	
ESSENTIAL	Placebo *v* enoximone (β blocker treated patients)
Metabolic agents	
Ranolazine	Placebo *v* ranolazine
Normal LVEF congestive heart failure	
Neurohumoral antagonists	
CHARM Preserved	Placebo *v* candesartan
I-PRESERVE	Placebo *v* irbesartan
PEP-CHF	Placebo *v* perindopril
SENIORS	Placebo *v* nebivolol

*See box at end of article for explanation of trial acronyms.
†New treatments tested against conventional background therapy (diuretic, digoxin, ACE inhibitor, β blocker) unless stated otherwise.
‡Recently terminated prematurely because of "futility".
ACE, angiotensin converting enzyme; LVEF, left ventricular ejection fraction.
Adapted from McMurry J, Pfeffer MH. *Circulation* 2002;**105**:2099–106.

Trial acronyms

CHARM: Candesartan in Heart Failure-Assessment of Reduction in Mortality and morbidity
COMET: Carvedilol Or Metoprolol European Trial
ECHOS: The Echo Cardiography and Heart Outcome Study
ENABLE: ENdothelin Antagonist Bosentan for Lowering cardiac Events
ESSENTIAL: ThE StudieS of oral Enoximone Therapy In Advanced heart faiLure
IMPRESS: Inhibition of MetalloProtease by BMS-186716 in a Randomized Exercise and Symptoms Study
MERIT-HF: Metoprolol CR/XL Randomised Intervention Trial in congestive Heart Failure
MOXCON: MOXonidine in CONgestive heart failure
OVERTURE: Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events
RECOVER: Research into Etanercept CytOkine Antagonism in VEntriculaR dysfunction trial
REMATCH: Randomized Evaluation of Mechanical Assistance for Treatment of Chronic Heart
RENAISSANCE: Randomized Etanercept North AmerIcan Strategy to Study ANtagonism of CytokinEs
RENEWAL: Randomized Etanercept Worldwide evALuation
SCD-HeFT: Sudden Cardiac Death in Heart Failure
SENIORS: Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors
WATCH: Warfarin Antiplatelet Therapy in Chronic Heart failure

with a different anticytokine agent (the antichimeric monoclonal antibody, infliximab), was also recently stopped early, because of an increased risk of death or hospitalisation in the active treatment group.

Other ongoing phase III trials are summarised in table 1.

OTHER POTENTIAL FUTURE TREATMENTS FOR HEART FAILURE

So far treatments in phase III, morbidity mortality trials, have been discussed (table 1). There are, however, also many more treatments in an earlier stage of development. These include new neurohumoral antagonists (for example, arginine vasopressin antagonists),[54][55] inotropes (for example, levosimendan, low dose enoximone used in combination with a β blocker),[56][57] and agents targeted at anaemia (erythropoietin and erythropoietin-like compounds)[58] and renal dysfunction (adenosine agonists).[59] There is also interest in matrix-metalloprotease inhibitors,[60] new antiarrhythmic agents (for example, dronedarone),[61] growth hormone, and metabolic interventions (for example with ranolazine, a partial fatty acid oxidation inhibitor which may improve myocardial metabolism and reduce myocardial ischaemia).[62]

Outwith the scope of this review are gene therapy and cell therapy offering the prospect of tailored treatment and the replacement of dead myocytes (and the reversal of CHF), respectively.[63]

Similarly, devices and surgery look more promising than ever before. Small studies with biventricular/multi-site pacing ("resynchronisation therapy") have been positive, and larger morbidity/mortality trials are underway. Implantable cardioverter-defibrillators (ICDs) have also proven to be remarkably effective in survivors of myocardial infarction with left ventricular systolic dysfunction.[64][65] The results of the SCD-HeFT trial of ICD therapy in CHF are awaited.[64][65]

The REMATCH trial has recently shown that a left ventricular assist device can increase survival in patients with severe, intractable, CHF.[66] Many technical problems remain with these devices and complication rates are high. Improvements must, however, surely come soon.

Heart replacement (as opposed to support) is, of course, another option in end stage CHF. Cloning techniques are bringing the possibility of xenotransplantation closer. Clinical trials of total artificial hearts (for example, Abio-cor) are also underway.

More conventional surgical approaches are also being systematically studied. In the UK there is a randomised trial of "coronary revascularisation" underway (percutaneous coronary intervention or bypass surgery), and another trial is planned in the USA looking at bypass surgery alone or in combination with reconstructive surgery (for example, mitral valve repair or left ventricular remodelling).

Many other important questions cannot be discussed here in detail. They include the clinically pressing problem of adding ever more treatments to a patient's existing treatment. Can we ethically find ways of comparing proven treatments to new ones (even though that will mean patients not receiving proven treatment in the course of a randomised trial)? Can we target therapies? Will our greater understanding of the human genome help here? But will the sponsors of large trials, the pharmaceutical industry, encourage targeting of therapy? What clinical, ethical, and moral questions will the molecular revolution pose in heart failure (think, for example, about implantation of fetal myocytes or stem cells into the failing myocardium). Drug development in heart failure will certainly be as challenging in the next 20 years as it has been in the past two decades. Indeed, as more effective treatments improve prognosis and, therefore, reduce event rates, conventional clinical trials with mortality or mortality/morbidity end points may become enormously large and prohibitively expensive. We may not only need to think of new approaches to trial design but also new end points for trials, perhaps refocussing on patient well being rather than adverse clinical events.

Finally, this review has focused on symptomatic heart failure caused by left ventricular systolic dysfunction. Many patients have symptomatic heart failure but preserved systolic function; others have impaired left ventricular function but no symptoms. We really do not, yet, know how to treat these patients. Trials are, however, underway to find the answer to this question.[67]

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Correspondence to: Professor John JV McMurray, Department of Cardiology, Western Infirmary, Glasgow G11 6NT, UK; j.mcmurray@bio.gla.ac.uk

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QUESTION AND ANSWER SESSION

Question: What is the state of play with xenografts?

Professor McMurray: Basically, in most countries, xenotransplantation has been discontinued. This is particularly so in this country because of fear of transmission of organisms from animals to humans. Obviously, the BSE [bovine spongiform encephalopathy] issue has made people very scared about xenotransplantation.

Question: Much as we, like many other people, like gene therapy and cell therapy, don't you think that both are more likely to be of benefit in 20 years' time rather than 10 years' time.

Professor McMurray: I think in terms of delivery, in terms of evidence, and in terms of safety, cell therapy looks a lot more promising than gene therapy at the moment, even though it started later.

Question: The thing that I would like most in heart failure is not to have to go through notes, not to have to fiddle with some computer. I want a little card that has on it the ECG, the chest x ray, the coronary angiogram, the echo and a nice MR picture on it, along with all the recent biochemistry, all nicely tabulated by date. I think a simple thing like that would actually have more impact on heart failure in the next five years than many of the other things. We could also include treatment so that for every single patient you could record exactly what is happening and what all the baseline details are. This would allow a very easy audit.

Professor McMurray: You are absolutely right. I would have said if we were giving this talk 10 years ago we might have said information technology was going to impact in a way that so far it has failed to do. But I am sure that it is around the corner.

Question: You didn't predict the complete eradication of coronary heart disease and thus making the diagnosis of heart failure extinct.

Professor McMurray: I was very intrigued by the health survey for Scotland for 1998, which was published at the end of last year. It showed that there was a substantial increase in the number of individuals in the population with coronary heart disease compared with the previous survey in 1995. That doesn't surprise me or other clinicians, but I think it might surprise some of our administrators and those in government. We are not going to eradicate coronary disease. The incidence of coronary disease, at least in young patients, is falling but in terms of the absolute numbers of people in the population with chronic coronary heart disease the numbers are going up and will continue to go up for the next 20 years at least. There is nothing we can do about it because those patients have already got atheroma and we are not going to make it go away. So chronic coronary disease and heart failure are going to become more common.

Question: Even if you did eradicate coronary heart disease, would you eradicate heart failure? I would argue that actually heart failure, loss of myocytes, loss of function, and weakening of the heart is actually part of the aging process. So unless we understand the biology of that and why the cells are lost, and whether we can control that and actually induce division of myocytes, then we are actually going to be stuck with heart failure. It may that the cause will change but I think that we are going to be in business for a long time.

Professor McMurray: We are certainly going to be stuck with diastolic heart failure.

Question: Are you as despondent as I am? It seems to me that it takes ever longer to get the results of clinical trials into everyday practice, with more and more hurdles in the way, such as licensing and NICE [National Institute for Clinical Excellence]. In the next 10 years will we get faster, and better, at doing this?

Professor McMurray: I'm absolutely convinced we will, and I'm not as despondent as you are. I think the β blocker story is tremendous, though maybe not in the UK. If you look across Europe you will see rates of 40–50% use in other countries. We have been lucky enough to be involved in a whole sequence of trials in recent years and we have been tracking the rate of use of β blockers. In 1998 about 10–15% of patients in trials were getting β blockers; we are now looking at the trials that have just completed randomising and it is about 55–60%. That is a tremendous rate of change. Admittedly it is in specialist centres but it is a much more rapid rate of change than I think we saw before with ACE inhibitors.

Question: As a general practitioner, I have many elderly patients over 75 with shortness of breath, in whom chest x ray and ECG are remarkably normal. What should we do with these patients?

Professor McMurray: I wouldn't stop at a chest x ray and ECG. The two main causes of breathlessness are either lung disease or cardiac disease, so I would consider further investigation, in other words echocardiography and pulmonary function tests. If the patient has otherwise inexplicable breathlessness, then they deserve proper investigation.

Question: Given the resources available in general practice, when should we consider a coronary angiogram in a heart failure patient with absolutely no evidence of angina?

Professor McMurray: I have a low threshold for coronary angiography but I work in a different service setting than most. I wouldn't consider a coronary angiogram in a heart failure patient, other than for research purposes, unless I thought that it might lead to some treatment intervention that would influence the patient's outcome. Coronary angiography is an invasive investigation and it does have problems, so there is no point in doing it unless you are going to act upon the results of it in some way that might improve outcome. Unless you are thinking about percutaneous coronary intervention or coronary artery bypass grafting then there are very few other reasons why you might want to establish the diagnosis of coronary artery disease with certainty.

Comment (Professor Wood): There are two issues really. The first is that these patients almost certainly have got coronary disease. If you've attributed their heart failure to some other aetiology, you are going to be wrong in about one in two cases, so actually if you want a diagnosis and you need to exclude coronary artery disease then an angiogram is essential. But the second issue is whether that information will affect your management. We have demonstrated that in a proportion of these patients, there was evidence of hibernating myocardium and they were managed by revascularisation, so we raised the argument that actually there may be a case for doing angiography routinely in patients with heart failure because some of them would be eligible for revascularisation.

Professor McMurray: But do you really believe that in a 77 year old who doesn't have angina that you would want to do a coronary angiogram to think about percutaneous intervention or coronary artery bypass grafting?

Comment (Professor Poole-Wilson): In the ATLAS study there was postmortem material in 170 odd patients and it was very humbling. We get the diagnosis wrong in heart failure quite often. In Europe, they are surprised that we don't do angiograms in nearly all our patients with heart failure.

Comment (Professor Cowie): I don't think we've got enough evidence to be systematic and say that doing coronary angiography in all new cases of heart failure is going to have any effect on outcome in that group of patients. We need more data to suggest that routine angiography and revascularisation and hibernation studies makes a difference. We can't answer the question at the moment.

Question: We've heard today that there is no role for atenolol in heart failure. None of the trials have used it, and presumably that's because it is generic and there is no money in it. But if we have a patient who is on atenolol for another reason, such as hypertension, would you stop it and start another one?

Professor McMurray: I absolutely would *not* stop atenolol if the patient were already on it. The only reason not to use atenolol in heart failure is because you don't have the appropriate starting dose. So if you see a patient not on a β blocker and you have to start them on a β blocker, you need to start with a low dose β blocker, and the only ones that we know about are bisoprolol, carvedilol, and metoprolol—you can't start with atenolol as we don't know what dose to use, and you don't have the very low doses available.

Comment (Professor Poole-Wilson): In our hospital we were worried that we use so little β blocker until we looked at the problem the other way around and looked at how many people were on diuretics and on atenolol. Of course, they started the atenolol for angina and then got onto a diuretic,

and we had masses of them, so if instead of calling it angina we called it heart failure then they were all on β blockers and the numbers go up.

Question: Regarding the data for prevention of heart failure by thrombolysing inferior acute myocardial infarction, we know that the number needed to treat to reduce mortality is over 100. But are there any data showing that by thrombolysing an acute inferior myocardial infarction that we in fact reduce morbidity from heart failure and arrhythmias?

Professor Cowie: I think John Rawles' data from the GREAT study in the north-east of Scotland, which looked at early thrombolysis by GPs versus waiting to thrombolyse in hospital, definitely showed that early thrombolysis improves LV function when assessed subsequently and improves mortality and hospitalisation. This is much more the case for anterior infarcts, as you'd expect, but the data such as there are also suggest some benefit in inferior infarcts.

Professor McMurray: You wouldn't even have to have an infarct to prevent heart failure. The CURE study shows in unstable angina and non-Q wave myocardial infarction that clopidogrel actually reduced the incidence of heart failure.

Question: What is your view on the drug trials and the problem of polypharmacy? Normally, when you are testing a treatment, you take a standard treatment and test the new treatment against it. In heart failure, for some reason, we have got into this "on top of" mode of thinking, so that every trial is testing a new drug not against the current best treatment, but on top of it. Is this something that is really stopping progress in this area? An extreme example would be that nobody has tried a β blocker against an ACE inhibitor, which might allow us to reduce one drug if we could decide which patients would be better on which drug. What is your view on that?

Professor McMurray: My view is that I haven't been clever enough to think of the answer to the ethics committees that won't allow us to do this. They insist that we cannot withhold evidence based therapy from patients with heart failure. There has obviously been a chink in the armour recently in that the angiotensin receptor blocker studies have been allowed to substitute for an ACE inhibitor and compare head to head with an ACE inhibitor, so drugs that are similar in action have been compared head to head with proven therapy, so there has been a little bit of progress, but when it comes to comparing a drug that is completely different to an established therapy we have made no progress and I don't know how we are going to. But we certainly need to, whether it be in patients who are intolerant of the treatment or whatever.

Comment (Professor Poole-Wilson): I don't understand the ethical argument. You could argue that by not doing that study you are actually, unbeknownst to yourself, harming the patient, as you don't know the reverse. There are, for example, some drugs that have been shown not to work but it could have been because they were used in combination with other drugs. It seems to me there is a certain amount of equipoise in the ethical argument.

Professor McMurray: It is certainly something we have all been thinking about. It would be nice someday to sit down and set out all the ethical arguments for and against.

Question: We have heard today about BNP, and that it is "almost there". I just wondered what else is needed and when we are going to have it?

Professor McMurray: There are more studies underway, but I think the issue is that most of the studies to date have not been large enough, and have not been carried out in representative enough populations to know whether the test is truly doing what we would like it to do.